INTRODUCTION

Oral Bioavailability Enhancement of Lovastatin

The therapeutic effectiveness of a drug depends upon the ability of the delivery system to make available the pharmacologically active moiety to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. This feature of the delivery system is referred to as physiologic or biologic availability or still simply bioavailability. For a large number of drugs, a pharmacologic response can be related directly to the plasma levels.

Thus the term bioavailability is defined as “the rate and extent (amount) of absorption of unchanged drug from its dosage form”. It can also be defined as “the rate and the extent to which the ingredients or active moiety is absorbed from the drug product and becomes available at the site of action”[1].

Drug Solubility and Biopharmaceutics classification Scheme of Drugs

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for anticipated pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% new chemical entities (NCEs) developed in pharmaceutical industry are practically insoluble in water[2]. Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, and solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, its dose, site of absorption, its half life and required dosage form characteristics[3].

The Biopharmaceutics Classification System (BCS) is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. This system restricts the prediction using the parameters solubility and intestinal permeability.

A biopharmaceutics drug classification scheme for correlating *in vitro* drug product dissolution and *in vivo* bioavailability was proposed by Amidon *et al.*, based on

recognization that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption[4]. This analysis uses a transport model and human permeability results for estimating *in vivo* drug absorption to illustrate the primary importance of solubility and permeability on drug absorption.

On the basis of these solubility and permeability characteristics can be classified in one of the four possible categories, as indicated in Table 1.

Table 1: The Biopharmaceutics classification scheme

Class I	**Class II**
High Solubility High Permeability	Low Solubility High Permeability
Class III	**Class IV**
High Solubility Low Permeability	Low Solubility Low Permeability

Bioavailability Enhancement of poorly water-soluble drugs

Oral bioavailability enhancement of poorly water-soluble BCS class II drugs is considered as a difficult task in formulation development. As indicated by Table 1, these drugs have low solubility and high permeability.

Literature cites various methods to enhance the solubility of poorly water-soluble drugs. These are, *Viz.* Micronization, Micellar Solubilization, Salt formation, Soluble Prodrugs, Metastable polymorphs, Inclusion complexes, Solid dispersions, Nanosuspensions, Adsorbents, Microemulsions, Cosolvents, Spherical Agglomeration or Crystallization, Crosslinkage with polymers, etc[3].

Dissolution of drug is the rate determining step for oral absorption of the poorly water-soluble drugs like Lovastatin; however the solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of these drugs.

Hence, the present study is planned to identify suitable techniques of solubility enhancement of a Cardiovascular drug i.e. Lovastatin as the key to ensure the goals of a good formulation like good oral bioavailability, reduced frequency of dosing and better patient compliance combined with a low cost of production.

The fact that dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release etc., will also impose constraints in the selection of suitable method and finally regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy etc., are also to be kept in mind before proceeding for research.

Establishment of *In Silico* Quantitative Structure Pharmacokinetic Relationships among Cardiovascular Drugs

The pharmaceutical industry has been late in recognizing that undesirable absorption, distribution, metabolism and excretion (ADME) of new drug candidates are the major cause(s) of many clinical phase trial failures. Identification of the fact has resulted in a refined and more scientific approach for launching drugs for patient needs. Accordingly, it has been an endeavor of the pharmaceutical scientists to design new drug molecules realistically predicting their pharmacokinetic and pharmacodynamic characteristics prior to their synthesis[5].

It has been accepted by the research laboratories that the drug discovery and development using the conventional approaches of random screening have proved to be quite time consuming and expensive. This has resulted in a paradigm shift to identify such problems early during the drug discovery process. Apart from the scientific interest, there are economic considerations as well, as out of numerous compounds synthesized; only a few eventually reach the market as a new drug. A sizable proportion of drug candidates fail during clinical trials because of poor pharmacokinetic (i.e., ADME) properties. This is an economic disaster, as the failed drugs have been in pipeline for several years, with the large amounts of effort and money invested in their development. Hence, the focus of drug development has widely expanded to include procedures aimed at identifying potential failures as well as successes[5, 6].

More recently, *in silico* Quantitative Structure Pharmacokinetic Relationships (QSPkR) modelling has been investigated as a tool to optimize selection of the most suitable drug candidates for development. Being able to predict ADME properties quickly using computational means is of great importance, as experimental ADME testing is both expensive and arduous yielding low productivity. The use of computational models in the

prediction of ADME properties has been growing rapidly in drug discovery, as they provide immense benefits in throughput and early application of drug design[5-7].

The *in vitro* approaches are widely practiced to investigate the ADME properties of new chemical entities. Most of such ADME properties are pictorially depicted in Fig 1.

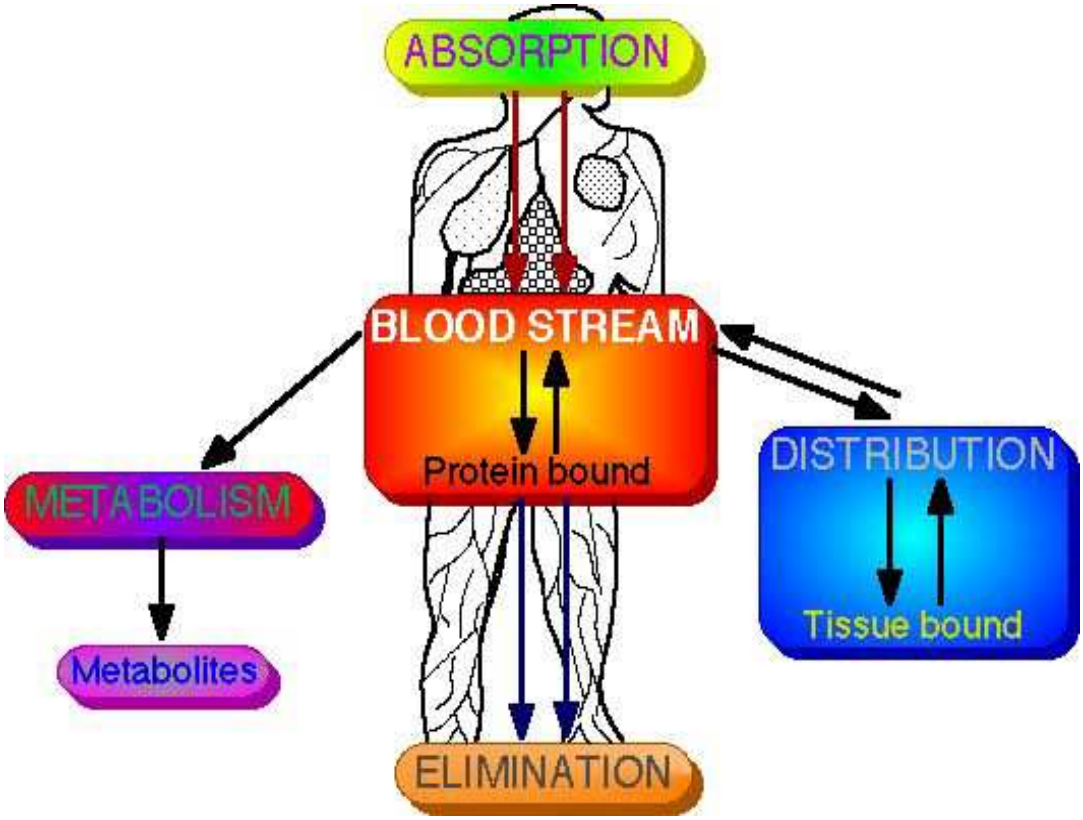

Fig. 1: Various ADME processes during drug sojourn in human body[5]

Cardiovascular drugs are very useful for therapeutic interventions to cure diseases affecting the physiology and anatomy of a normal heart. For the present study Cardiovascular drugs are selected for QSPkR investigations as this category of drugs consist of significant number of compounds for thorough investigation in their pharmacokinetic performance. Moreover, congeners of this class have many common pharmacokinetic characteristics, mechanism and degree of affinity with body tissues, etc. Also, important descriptors like experimental log P, melting point, molecular weight etc. of these drugs are known and are available in standard texts or journals[5, 6].

In the light of above background, this study is undertaken to investigate suitability of some bioavailability enhancement techniques to enhance the bioavailability of a

cardiovascular drug i.e. Lovastatin and to find out *in silico* ADME predictions of cardiovascular drugs using quantitative structure pharmacokinetic relationships.

This study will be very useful for future scientists as Lovastatin, being useful for the treatment of dyslipidemia and the prevention of cardiovascular diseases is clinically useful and by enhancing its Bioavailability, patient compliance can be improved and the total therapeutic dose of the drug can be reduced because due to enhanced dissolution profile, therapeutically appreciable amount of Lovastatin can be made available at the site of action from a lesser administered Lovastatin dose.

Secondly, from the Pharmacokinetic DATA of cardiovascular drugs that will be collected from literature, quantitative structure Pharmacokinetic relationships will be established so as to make some recommendations for the discovery of some novel cardiovascular compounds by pharmaceutical scientists in future.

LITERATURE REVIEW

Miyazawa *et al.*, (1995)[8] cited that δ-Cyclodextrin (CD) is a cyclic oligosaccharide composed of nine α-l, 4-linked D-glucose units. They observed that aqueous solubility of δ-CD was greater than that of β-CD but less than that of α-CD or γ,-CD and by them no surface activity of δ-CD was observed. δ-CD did not exhibit any hemolytic activity at 4.0 × 10^{-2} M δ-CD, which was close to its saturated solution. The acid-catalyzed hydrolysis increased in the following order: α-CD <β-CD < γ-CD < δ-CD. According to them δ-CD did not show any significant solubilization effect on most of the slightly soluble or insoluble drugs in water. However, in the case of a large guest molecule such as spironolactone (SP) and digitoxin, which have a steroidal framework, they reported that the enhancement of solubility of the guest molecule by δ-CD was greater than that by α-CD. The solubility of SP increased about 30-fold in the presence of δ-CD (4.5 × 10^{-2} M).

Jachowicz and Nurnberg, (1997)[9] prepared solid dispersions of different ratios of Gelita collagel as the carrier and lactose by the spray drying method. Dissolution studies have shown that by preparing solid dispersions the dissolution rate and the solubility of Oxazepam increased markedly, independent of the ratio of drug, carrier and lactose. The properties of the solid dispersions were characterized by X-ray diffraction and polarizing microscopic studies. An amorphous form of all prepared solid dispersions was indicated in X-ray studies. Tablets of solid dispersions of Oxazepam: Gelita Collagel, physical mixtures and the drug alone were prepared. The best results from the dissolution profiles were obtained for tablets containing solid dispersions. According to them tablets remained in good physical properties when stored for one year in normal conditions.

Stella *et al.*, (1999)[10] have addressed the issues of the mechanisms of drug release from Cyclodextrin complexes. More specifically, they attempted to answer the question whether drug release from aqueous formulations is slow or incomplete? An assessment of the literature, their own work and various simulations suggests that drug release from Cyclodextrin complexes is rapid and quantitative in most cases. After parenteral administration, it does appear that cyclodextrins might cause some alterations in the fraction of free drug eliminated in the urine during that time frame where the Cyclodextrin itself is undergoing substantial renal clearance.

Archontaki *et al.*, (2002)[11] studied the solubility enhancement of the water insoluble bromazepam during the formation of its inclusion complexes with β-Cyclodextrin (β-CD) and β-hydroxypropyl-Cyclodextrin (β--HP-CD). The phase solubility technique established by **Higuchi and Connors (1965)**[12] and UV-spectrophotometric methods (zero- and second-order derivative approaches) were used to measure the changes introduced in this chemical system. The amount of time, which was necessary to reach equilibrium between inclusion complexes and their free components, was estimated and found equal to 24 h. The study was carried out at (i) pH 7.0 and 25 °C and (ii) pH 7.4 and 37 °C. They found that solubility of bromazepam increased linearly as a function of concentration for both β-and β-hydroxypropyl-cyclodextrins.

Turk *et al.*, (2002)[13] studied micronization of pharmaceutical substances by the rapid expansion of supercritical solutions (RESS) process and suggested it as a promising method to improve bioavailability of poorly soluble pharmaceutical agents. According to them, RESS process enables the micronization of thermally labile materials and the formation of particles of less than 500 nm in diameter. Their research aimed towards an improved understanding of the relationship between process parameters and particle characteristics and to explore new areas of application for nanoscale particles. From experimental findings they showed that the RESS processing of Griseofulvin leads to a significantly better dissolution rate of the drug resulting in an improved bioavailability. Moreover, stable suspensions of nanoscale particles of β-Sitosterol were produced by the rapid expansion of a supercritical mixture through a capillary nozzle into aqueous solutions. The particle sizes of β-Sitosterol in the aqueous solution were smaller or equal to those produced by RESS into air without the surfactant solution.

Joshi *et al.*, (2004)[14] reported that oral bioavailability of a poorly water-soluble drug can be greatly enhanced by using its solid dispersion in a surface-active carrier. The weakly basic drug (p*K*a ~5.5) had the highest solubility of 0.1 mg/ml at pH 1.5, <1µg/ml aqueous solubility between pH 3.5 and 5.5 at 24 ± 1 °C, and no detectable solubility (<0.02µg/ml) at pH greater than 5.5. By making two solid dispersion formulations of the drug, one **in Gelucire 44/14®** and another one in a mixture of polyethylene glycol 3350 (PEG 3350) with polysorbate 80, by dissolving the drug in the molten carrier (65°C) and filling the melt in hard gelatin capsules. From the two solid dispersion formulations, the

PEG 3350–polysorbate 80 was selected for further development. The solid dispersion provided a 21-fold increase in bioavailability of the drug as compared to the capsule containing micronized drug. It was hypothesized that polysorbate 80 ensured complete release of drug in a metastable finely dispersed state having a large surface area, which facilitates further solubilization by bile acids in the GI tract and the absorption into the enterocytes.

Thus, the bioavailability of this poorly water-soluble drug was greatly enhanced by formulation as a solid dispersion in a surface-active carrier.

Hecq *et al.*, (2005)[15] prepared and characterized nanocrystals for investigating solubility and dissolution rate enhancement of Nifedipine. In order to enhance these characteristics, the preparation of nifedipine nanoparticles was achieved using high pressure homogenization (HPH). They optimized homogenization procedure in regard to particle size and size distribution. They conducted crystalline state evaluation before and following particle size reduction through differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to denote eventual transformation to amorphous state during the homogenization process. Through this study, they have shown that initial crystalline state is maintained following particle size reduction and that the dissolution characteristics of nifedipine nanoparticles were significantly increased in regards to the commercial product.

Shoyele and Cawthorne (2006)[16] have reviewed particle engineering techniques for formulation of biopharmaceuticals for pulmonary delivery which is faced with the challenge of producing particles with the optimal properties for deep lung deposition without altering the native conformation of these molecules. They have stressed that traditional techniques such as milling are continuously being improved while newer and more advanced techniques such as spray drying, spray freeze drying and supercritical fluid technology are being developed so as to optimize pulmonary delivery of biopharmaceuticals. They have found that while some of these techniques are quite promising, some are harsh and impracticable and the choice of a technique depends on consideration of method scale up, cost-effectiveness and safety issues.

Jun *et al.*, (2007)[17] studied the practically insoluble drug, simvastatin (SV), and its inclusion complex with hydroxypropyl- β-Cyclodextrin (HP-β-CD) prepared using

supercritical antisolvent (SAS) process, investigating to improve the aqueous solubility and the dissolution rate of drug, thus enhancing its bioavailability. They concluded that SAS process could be a useful method for the preparation of the inclusion complex of drug with HP-β-CD and its solubility, dissolution rate and hypolipidemic activity is significantly increased by complexation between SV and HP-β-CD.

Allaboun *et al.*, (2007)[18] investigated the influence of micelle-drug solubilization on the dissolution rate of monodispersed particles of benzocaine. A model describing and predicting the initial dissolution rates of spherical particles was derived starting from the boundary layer theory.

The dissolution rate of benzocaine spherical particles was determined in water and in solutions of sodium lauryl sulfate (SLS) under static conditions. The derived model was applied to the experimental data. The diffusion coefficients and the aqueous diffusion layer values were estimated from the experimental results and the aforementioned model. Obvious deviation was observed at high micellar concentrations. The results obtained from this study suggested that it is possible to predict the initial dissolution rates of monodispersed particles in micellar systems.

Overhoff *et al.*, (2007)[19] developed an ultra-rapid freezing (URF) technology to produce high surface area powders composed of solid solutions of an active pharmaceutical ingredient (API) and a polymer stabilizer. A solution of API and polymer excipients (s) is spread on a cold solid surface to form a thin film that freezes in 50 ms to 1 s. They established that the ability to produce amorphous high surface area powders with submicron primary particles with a simple ultra-rapid freezing process is of practical interest in particle engineering to increase dissolution rates, and ultimately bioavailability.

Blagden *et al.*, (2007)[20] stated that although numerous strategies exist for enhancing the bioavailability of drugs with low aqueous solubility, the success of these approaches is not yet able to be guaranteed and is greatly dependent on the physical and chemical nature of the molecules being developed. According to them crystal engineering offers a number of routes to improved solubility and dissolution rate which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients.

Yasuji *et al.*, (2008)[21]. Subjected some drugs to micronization or prepared as composite particles using supercritical fluid (SCF) technology with carbon dioxide (CO_2) for improving the dissolution properties of poorly water-soluble drugs. Solubility in CO_2 is the key when using this method. They suggested that the SC-CO_2 can improve the solubility of poorly water-soluble drug substances using few or no organic solvents and with little or no heating.

Sauceau *et al.*, (2008)[22] prepared piroxicam-β-Cyclodextrin complexes at solid state by means of supercritical carbon dioxide and studied the influence of temperature, residence time, water content and a ternary agent i.e. l-lysine. The complex was characterized by Differential Scanning Calorimetry, Scanning Electronic Microscope and dissolution profile in water. Finally, a complete inclusion was achieved for a piroxicam-β-Cyclodextrin-l-lysine mixture by keeping a physical mixture of the three compounds (1:2:1.5 molar ratio) for 2 h in contact with CO_2 at 150°C and 15 MPa. This technique they got enhanced dissolution rate, the stability, the solubility and the bioavailability of a piroxicam.

Dolenc *et al.*, (2009)[23] have examined the critical issues regarding engineering of a nanosuspension tailored to increase drug dissolution rate and its transformation into dry powder suitable for tableting. They produced nanosuspensions of Celecoxib, a selective COX-2 inhibitor with low water solubility, by the emulsion-diffusion method using three different stabilizers (Tween R 80, PVP K-30 and SDS). Spray-dried nanosuspension was blended with microcrystalline cellulose, and compressed to tablets. The selection of solvent and stabilizers was critical, firstly to achieve controlled crystallization and size, and secondly to increase the wettability of the hydrophobic drug. The crystalline nanosized Celecoxib alone or in tablets showed a dramatic increase of dissolution rate (Bioavailability enhancement) and extent compared to micronize one. Markedly lower compaction forces were needed for nanosized compared to micro-sized Celecoxib to produce tablets of equal tensile strength.

Chakraborty *et al.*, (2009)[24] communicated an in-depth discussion on the role of lipids (both endogenous and exogenous) in bioavailability enhancement of poorly soluble drugs, mechanisms involved therein, approaches in the design of lipid-based oral drug delivery systems with particular emphasis on solid dosage forms, understanding of

morphological characteristics of lipids upon digestion, *in vitro* lipid digestion models, *in vivo* studies and *in vitro–in vivo* correlation. They proposed that lipids as carriers, in their various forms, have the potential of providing endless opportunities in the area of drug delivery due to their ability to enhance gastrointestinal solubilization and absorption via selective lymphatic uptake of poorly bioavailable drugs.

Kumar *et al.*, (2011)[3] have reviewed solubility enhancement techniques for hydrophobic drugs and found that among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach market due to their poor aqueous solubility. For orally administered drugs solubility is one of the rate limiting parameters to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the development of pharmaceutical products. They devoted their review devoted to various traditional and novel techniques for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development.

Raval and Patel, (2011)[25] prepared stable nanoparticles with an aim to enhance dissolution of poorly water-soluble meloxicam, by combining antisolvent precipitation and high pressure homogenization approaches in presence of stabilizers (HPMC E5, SDS) and converting into dry powders by spray-drying.and characterized by preparing nanoparticles. These nanoparticles were characterized by SEM, XRD, FT-IR, and DSC as well as measuring the particle size and *in-vitro* drug dissolution. The DSC and XRD results indicated that the antisolvent precipitation process led to the amorphization of meloxicam. An increase in the stability of the nanoparticles was also assured by the sufficient adsorption of the stabilizers onto the drug surface. Meloxicam nanoparticles increased the saturation solubility of drug almost fourfold. The *in vitro* studies at Q5min showed a marked increase in the drug release from just 7% (raw drug) to 82% (Meloxicam nanoparticles). They concluded that combining of both the methods was a promising method to produce uniform and stable nanoparticles of meloxicam with remarkable improvement in dissolution rate due to an increased solubility by the effect of increased surface area and change to amorphous form of the drug. A combination of

HPMC E5 and SDS (2:1, w/w) was the most successful of all the stabilizing agents investigated as far as the formation of MLX suspensions were concerned.

Liu *et al.*, (2010)[26] aimed to enhance dissolution and oral bioavailability of poorly water-soluble Celecoxib (CXB) by preparing stable CXB nanoparticles using a promising method, meanwhile, investigating the mechanism of increasing dissolution of CXB. They concluded that the process by combining the antisolvent precipitation under sonication and HPH (high pressure homogenization) was a promising method to produce small, uniform and stable CXB (Celecoxib) nanoparticles with markedly enhanced dissolution rate and oral bioavailability due to an increased solubility that is attributed to a combination of amorphization and nanonization with increased surface area, improved wettability and reduced diffusion pathway.

Kawabata *et al.*, (2011)[27] stated that complete development works within a limited amount of time, the establishment of a suitable formulation strategy should be a key consideration for the pharmaceutical development of poorly water-soluble drugs. In this article, viable formulation options have been reviewed by them on the basis of the biopharmaceutics classification system of drug substances. Through this article they have described the basic approaches for poorly water-soluble drugs, such as crystal modification, micronization, amorphization, self-emulsification, Cyclodextrin complexation, and pH modification. They have provided literature-based examples of the formulation options for poorly water-soluble compounds and their practical application to marketed products. Classification of drug candidates based on their biopharmaceutical properties can provide an indication of the difficulty of drug development works. They recommended that a better understanding of the physicochemical and biopharmaceutical properties of drug substances and the limitations of each delivery option should lead to efficient formulation development for poorly water-soluble drugs.

Ekins *et al.*, (2000)[28] held a view that understanding the development of a scientific approach is a valuable exercise in gauging the potential directions the process could take in the future. By splitting short history of applying computational methods to ADME, they have described the evolution of these state approaches. Coming to the contemporary era they stressed on the need to accelerate drug discovery along with decreased economic inputs.

Fouchecourt *et al.*, (2001)[29] presented the existing methods in quantitative structure–pharmacokinetic relationship (QSPkR) modelling along with examples using chemicals of toxicological significance. They have suggested an alternative approach that involves the development of quantitative structure–property relationship (QSPR) models for parameters, blood: air partition coefficient, tissue: blood partition coefficient, maximal velocity for metabolism and Michaelis affinity constant, of physiologically-based pharmacokinetic (PBPK) models which are useful for conducting species, route, dose and scenario extrapolations of the tissue dose of chemicals.

They suggested that integrated QSPR–PBPK modelling should facilitate the identification of chemicals of a family that possess desired properties of bioaccumulation and blood concentration profile in both test animals and humans.

Graaf and Sinko, (12002)[30] the aim of their study was to investigate the feasibility of a quantitative structure-pharmacokinetic relationships (QSPkR) method based on contemporary three-dimensional (3D) molecular characterization and multivariate statistical analysis. They developed a multivariate 3D QSPKR model that could adequately predict overall pharmacokinetic behavior of adenosine A1 receptor agonists in rat. They recommended that this methodology can also be used for other classes of compounds and may facilitate the further integration of QSPkR in drug discovery and preclinical development.

Turner *et al.*, (2003)[31] envisaged the research on multiple pharmacokinetic parameter prediction for a series of cephalosporins and constructed a multiple-output artificial neural network model to predict human half-life, renal and total body clearance, fraction excreted in urine, volume of distribution, and fraction bound to plasma proteins for a series of cephalosporins.

Descriptors generated solely from drug structure were used as inputs for the model, and the six pharmacokinetic parameters were simultaneously predicted as outputs. The final 10 descriptor model contained sufficient information for successful predictions using both internal and external test compounds. Descriptors were found to contribute to individual pharmacokinetic parameters to differing extents, such that descriptor importance was independent of the relationships between pharmacokinetic parameters.

Their technique provides the advantage of simultaneous prediction of multiple parameters using information obtained by non-experimental means, with the potential for use during the early stages of drug development.

Turner *et al.*, (2004)[32] in their study made use of artificial neural networks (ANNs) for the prediction of clearances, fraction bound to plasma proteins, and volume of distribution of a series of structurally diverse compounds. A number of theoretical descriptors were generated from the drug structures and both automated and manual pruning were used to derive optimal subsets of descriptors for quantitative structure-pharmacokinetic relationship models. The combination of descriptor generation, ANNs, and the speed and success of this technique compared with conventional methods shows strong potential for use in pharmaceutical product development.

Yap *et al.*, (2006)[33] selected 503 compounds with known CL_{tot} described in the literature to establish quantitative structure–pharmacokinetic relationships for drug clearance by exploring three statistical learning methods, general regression neural network (GRNN), support vector regression (SVR) and k-nearest neighbour (KNN) for modeling the CL_{tot} of all of these known compounds. Six different sets of molecular descriptors, DS-MIXED, DS-3DMoRSE, DS-ATS, DS-GETAWAY, DS-RDF and DS-WHIM, were evaluated for their usefulness in the prediction of CL_{tot}. QSPkR models developed by using DS-MIXED, a collection of constitutional, geometrical, topological and electrotopological descriptors, generally give better prediction accuracies than those developed by using other descriptor sets. These results suggested that GRNN, SVR, and their consensus model are potentially useful for predicting QSPkR properties of drug leads.

Mager, (2006)[34] has closely reviewed quantitative structure-pharmacokinetic/pharmacodynamic relationships. Author has discussed traditional and contemporary approaches to developing QSPKR models along with selected examples of attempts to couple QSPkR and pharmacodynamic models to anticipate the intensity and time-course of the pharmacological effects of new or related compounds, or quantitative structure–pharmacodynamic relationships modeling. Considerable progress made in constructing empirical and mechanistic quantitative structure–Pk relationships (QSPkR)

along with diverse mechanism-based pharmacodynamic models of drug effects have been given due recognition by the author.

Singh *et al.*, (2007)[5] highlighted the increasing and expanding use of *in silico* approaches for successful prediction of pharmacokinetic properties of compounds during new drug discovery. They held the view that these techniques not only shorten the research-to-market cycle, but also eliminate the squandered effort in pharmaceutical R & D, thereby reducing the cost of drug development. These *in silico* models, for the prognosis of absorption, distribution, metabolism and excretion (ADME), are invariably based upon the implementation of quantitative structure pharmacokinetic relationship (QSPR) techniques. The information on diverse aspects of multivariate QSPR, however, lies scattered in diverse journals and books. The objective of article, therefore, was to furnish a broad overview of the key precepts of QSPkR and the subsequent advances.

Lee *et al.*,(2008)[35] aimed to elucidate the physicodynamic phenomena governing diffusion coefficient (*D*) of the loaded drugs in a female controlled drug delivery system (FcDDS) and to find the most influencing variable on the diffusivity using artificial neural networks (ANN). The release profiles of sodium dodecyl sulphate (SDS), a topical microbicide used as a model drug, from FcDDS were obtained using *in vitro* apparatus, the Stimulant Vaginal System (SVS), under various conditions. Among variables, pH of vaginal fluids was the most influencing factor in defining the diffusion coefficient (maximum value of 0.95±0.04) of SDS from FcDDS. The external exposure conditions clearly outweighed the effects of the formulation variables on the diffusion coefficient of SDS.

They suggested that a model-based approach can be used to assess the diffusion coefficient of loaded drugs in FcDDS under the given conditions, leading to a parameter-specific prevention strategy against sexually transmitted diseases (STD) with a high degree of confidence.

Nicolle *et al.*, (2009)[36] described the main types of inhibitors presently known for ABCG2, and how quantitative structure–activity relationship analysis among series of compounds may lead to build up molecular models and pharmacophores allowing to design lead inhibitors as future candidates for clinical trials. They specially drew

attention on flavonoid group which constitute a structurally-diverse class of compounds, well suited to identify potent ABCG2-specific inhibitors.

Yash Paul *et al.*, (2009)[37] conducted the study to investigate QSPkR for apparent volume of distribution (V_d) in man among 24 Quinolone drugs employing an extra thermodynamic approach. It is vital to predict the V d value of various drug leads during drug discovery so that compounds with poor bioavailability can be eliminated and those with an acceptable metabolic stability can be identified. Analysis of several thousands of QSPR correlations developed in the present study revealed an extremely high degree of cross-validated coefficient (Q^2) using the leave-one-out method ($P < 0.001$). Logarithmic transformation tends to improve the correlations marginally ($R^2 = 0.936$) but the inverse transform resulted in a distinct improvement in the correlation ($R^2 = 0.994$). Electronic and topological parameters were found to primarily ascribe the variation in V_d. Overall; the diffusional interactions were seemed to play a major role in attributing V_d rather than the permeational ones.

Yash Paul *et al.*, (2010)[38] conducted a study to investigate QSPkR for biological half-life (t1/2) in humans for 28 quinolone drugs employing extra-thermodynamic multi-linear regression analysis (MLRA) approach. The overall predictability was found to be high ($R^2 = 0.8752$, $F = 20.24$, $S^2 = 9.3212$, $Q^2 = 0.7384$, $p < 0.001$). Topological, steric and electrostatic parameters were found to primarily ascribe the variation in $t_{1/2}$. Logarithmic transformations of $t_{1/2}$ tend to improve the degree of correlations during one-parameter and two-parameter studies. However, the inverse transformations of $t_{1/2}$ remarkably enhanced the degree of correlations (both R^2 and Q^2). Maximum predictability for quinolones was found to be 94.16 %.

Goel *et al.*, (2011)[39] used 3D-QSPkR approach to obtain the quantitative structure pharmacokinetic relationship for a series of quinolone drugs (antimicrobial, particularly active against gram-negative organisms, especially *Pseudomonas aeruginosa*) using SOMFA (self organizing molecular field analysis). They investigated a series consisting of 28 molecules for their pharmacokinetic performance using biological half life ($t_{1/2}$) and obtained a statistically validated robust model for a diverse group of quinolone drugs having flexibility in structure and pharmacokinetic profile ($t_{1/2}$) using SOMFA having good cross-validated correlation coefficient r^2_{cv} (0.6847), non cross-validated correlation

coefficient r^2 values (0.7310) and high F-test value (33.9663). Analysis of 3D-QSPkR models through electrostatic and shape grids provided useful information about the shape and electrostatic potential contributions on $t_{1/2}$. The SOMFA results provided them with an insight for the generation of novel molecular architecture of quinolones with optimal half life and improved biological profile.

Yash Paul *et al.*, (2012)[40] conducted *in silico* Quantitative Structure Pharmacokinetic Relationship (QSPkR) Modeling on antidiabetic drugs to estimate serum protein binding (%SPB) for assessing the efficacy of drugs used to treat diabetes in patients. Using computer assisted Hansch approach they successfully established QSPkR for the prediction of %SPB in human for congeneric series of twenty antidiabetic drugs. Using an array of fitting statistical procedures they analysed the QSPkR correlations and validated using leave-one-out (LOO) approach. Their studies, after analysis revealed high degree of cross-validated coefficients (Q^2) using LOO method ($p<0.001$) and the overall predictability was found to be high %SPB ($R^2=0.9949$, $F=426.30$, $S^2=9.6266$, $Q^2=0.9957$, $p<0.001$). Serum protein binding (%SPB) was attributed to electrostatic and constitutional parameters. Its positive dependence on such descriptors indicates that hydrogen bonding and van der Waals' interactions play a stellar role in governing protein binding.

Louis and Agrawal, (2012)[41] developed a quantitative structure-pharmacokinetic relationship (QSPkR) model for the volume of distribution (*V*d) values of 126 anti-infective drugs in humans employing multiple linear regression (MLR), artificial neural network (ANN) and support vector regression (SVM) using theoretical molecular structural descriptors. A correlation-based feature selection (CFS) was employed to select the relevant descriptors for modeling.

The model results showed that the main factors governing *V*d of anti-infective drugs are 3D molecular representations of atomic van der Waals volumes and Sanderson electronegativities, number of aliphatic and aromatic amino groups, number of beta-lactam rings and topological 2D shape of the molecule. Model predictivity was evaluated by external validation, using a variety of statistical tests and the SVM model demonstrated better performance compared to other models. They suggested that the developed models can be used to predict the *V*d values of anti-infective drugs.

Zhivkova and Doytchinova (2012)[42] their study employed quantitative structure–pharmacokinetics relationships (QSPkR) to derive models for VD prediction of acidic drugs. The steady-state volume of distribution (VDss) values of 132 acidic drugs were collected, the chemical structures were described by 178 molecular descriptors, and QSPkR models were derived after variable selection by genetic algorithm and stepwise regression. Models were validated by cross-validation procedures and external test set. According to the molecular descriptors selected as the most predictive for VDss, the presence of seven- and nine-member cycles, atom type P^{5+}, SH groups, and large nonionized substituents increase the VDss, whereas atom types S^{2+} and S^{4+} and polar ionized substituents decrease it. Cross-validation and external validation studies on the QSPkR models derived in the present study showed good predictive ability with mean fold error values ranging from 1.58 (cross-validation) to 2.25 (external validation).

The model performance was comparable to more complicated methods requiring *in vitro* or *in vivo* experiments and superior to the existing QSPkR models concerning acidic drugs. Apart from the prediction of VD in human, these models are also useful as a curator of available pharmacokinetic databases.

Honey *et al.*, (2012)[43] stated that non-steroidal anti-inflammatory drug (NSAID) induced gastrointestinal toxicity has attracted greater attention over the years. The development of NSAIDs having safer therapeutic profile depends on the better understanding of their mechanisms, physicochemical and pharmacokinetic properties. Their investigation aimed at *in silico* three dimensional quantitative structure–pharmacokinetic relationship (3D-QSPkR) assessment of a group of NSAIDs using self-organizing molecular field analysis (SOMFA) approach. Their study illustrated the significance of structural variables in molecular architecture of NSAIDs especially etodolac for further optimization of ADMET properties with improved therapeutic profile.

OBJECTIVES

Present research entitled “Studies on Oral Bioavailability Enhancement of Lovastatin and establish *In Silico* Quantitative Structure Pharmacokinetic Relationships among Cardiovascular Drugs” has been envisaged to fulfill the following objectives:

1. To study *In Vitro* Oral Bioavailability Enhancement of Lovastatin by studying a few of the available bioavailability enhancement approaches. Lovastatin is a BCS class II drug and hence has a poor water solubility due to which its rate of solubilization is low. This drug has high permeability; therefore improvement in its solubility is expected to improve its bioavailability.
2. To establish *In Silico* Quantitative Structure Pharmacokinetic Relationships among Cardiovascular Drugs so that the involvement of animals, humans, wastage of money, etc. could be prevented on studies to be conducted on newly discovered cardiovascular drugs in future, as using this technique or establishing QSPkR among Cardiovascular drugs, we can predict Pharmacokinetic Parameters of the newly discovered cardiovascular drugs.

Hence, the important findings generated from present research being envisaged, can be evaluated for their utility in assessing new cardiovascular drugs that would fit pharmacokinetically in future successful clinical trials of new cardiovascular compounds.

WORK PLAN AND METHODOLOGY

1. Literature survey
2. Characterizations and Identification of Lovastatin
3. Selection of bioavailability enhancement technique/s
4. Selection of various reagents and polymers depending upon selected technique/s
5. Preparation of suitable formulation/s
6 Characterization of selected formulation/s
7. Structure uploadation of selected cardiovascular drugs on Chem Draw Ultra 7.0
8. Selection of Pharmacokinetic parameters of selected cardiovascular drugs
9. Computation of Descriptors Using Suitable Software
10. Application of multivariate statistical techniques using suitable software
11. Interpretations of Results
12. Compilation of DATA in the form of thesis

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